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A cosmic background image featuring a deep blue and purple nebula with wispy, ethereal structures. In the upper left, there's a bright, yellowish-white nebula. In the lower left, a bright, star-like object with a white and yellow glow is visible, surrounded by reddish-orange and yellowish clouds. The overall scene is a vast, colorful representation of outer space.

CHAPTER 10

Summary

The aim of the work presented in this thesis was to assess the short-term results after laparoscopic versus open surgical management of rectal cancer, the diagnostic performance of the sentinel-lymph-node procedure in colorectal cancer patients according to literature and to obtain insights in a new technique for sentinel-lymph-node mapping in colon cancer patients.

Laparoscopic rectal cancer resection

Laparoscopic surgery is considered to be an alternative to open surgery for curative treatment of patients with rectal cancer. Various studies^{1,2} have been performed to determine whether advantages for minimal invasive resection of rectal cancer exist. Although laparoscopic surgery has proven feasible in patients with rectal cancer, sufficient evidence demonstrating oncological safety is still not available (**Appendix I**). In 2004 the colorectal cancer laparoscopic or open resection (COLOR) study group undertook a non-inferiority phase III trial (COLOR II) at 30 centres worldwide. A total of 1103 rectal cancer patients were randomly assigned to either open or laparoscopic surgery. The short-term outcomes of the COLOR II trial are presented in this thesis (**Chapter 3**). Morbidity and mortality were similar in both groups. In the COLOR II trial 16% of laparoscopic surgeries were converted during surgery which is similar to most recent data.³ Patients who had laparoscopic surgery experienced benefits typical for minimally invasive surgery: less blood loss, less pain reflected by reduced dependence on epidural analgesia, earlier restoration of gastrointestinal function and a shorter length of hospital stay of one day. Adam et al.⁴ mentioned the importance considering the relationship between clear resection margins and risk of local recurrence. Results from the COLOR II show no significant difference in macroscopic completeness of resection and distal resection margin between laparoscopic and open resection. In 9% of all resection specimens in both groups a positive circumferential margin was found. Subgroup analysis of patients with low rectal cancer (within 5 cm of the anal verge) showed circumferential margin involvement in 9% whereas in the open group this was 21%. Nagtegaal and colleagues⁵ showed similar results after open surgery for low rectal cancer. They reported positive circumferential margins in 26.5% of the cases. Tumour involvement within or less than 1 mm of the circumferential margin was considered positive in the study by Nagtegaal et al. In accordance with an earlier report on Scandinavian data⁶ that 70-80 per cent of patients with tumours in the distal rectum were treated by abdominoperineal resection, three quarters of patients in the COLOR II trial with cancer of the distal 5 cm of the rectum had an abdominoperineal resection. Laparoscopic surgery for low rectal cancer appears to be associated with better circumferential mesorectal margins than open surgery, and our result of positive CRM in 9% without using extralevator excision for all abdominoperineal resection compares well to others reports. Technical benefits of laparoscopic surgery such as a magnified view and an improved illumination of the area, as well as, a better exposure of spaces not readily accessible to the surgeon's eye, may contribute to the reported results. Long-term data will show if laparoscopic surgery for rectal cancer localised within 5 cm from the anal verge result in less local recurrences compared to open surgery. Macroscopically complete mesorectal excisions were reported by the pathologist in 90% of all cases in the COLOR II trial. Since the first reports on laparoscopic total mesorectal excision for rectal cancer different rates of conversion have been reported. In **Chapter 4** the findings of a multicentre randomised controlled trial (COLOR II) about factors influencing conversion rate are presented. Results presented in the manuscript (**Chapter 4**), show that tumour location (>5 cm from anal verge) plays a role in the potential need to convert. When focussing on patient related factors several independent indicators were identified. Gender was not found to be an independent predictor

for conversion. Generally, the male pelvis is assumed to be narrower compared to the female pelvis, theoretically making the TME procedure more difficult and perhaps prone to conversion. Our data did not support this assumption. Other factors like age > 65 years and BMI were found to be correlated with the need for intraoperative conversion to open surgery. BMI in particular was a very strong predictive factor for conversion.⁷ BMI being an independent factor influencing conversion has been reported by several other trials.^{8,9} The need for conversion diminish the benefits of laparoscopic surgery versus primary open surgery. Conversion is significant associated with more postoperative complications compared to open surgery and is associated with longer operating times compared to patients who had their surgery laparoscopically. Outcomes as presented in **Chapter 4** are to be used in preoperative patients informed consent. Patients with a higher risk: age > 65 years with a BMI>25 and a tumour located between 5-15 cm from the anal verge should be informed about the higher risk of intraoperative conversion and it's downside effects.

Comparing different randomised trials regarding conversion rate is still very difficult because no worldwide accepted definition is accepted. In 2008 Shawski et al. published results of a web-based survey conducted among colorectal surgeons who represented members of both Society of American Gastrointestinal and endoscopic surgeons (SAGES) and American Society of Colon and Rectal Surgeons (ASCRS) to find out how they define conversion for laparoscopic colorectal surgery.¹⁰ After this survey it was concluded that it was considered clear that any incision made earlier than planned was deemed to be a conversion. But a footnote was made addressing the fact there are still many different views of conversion regarding incision length. In the COLOR II trial, a laparoscopic procedure was judged conversion to open surgery if dissection of the mesorectum was not completed laparoscopically.

Sentinel-lymph-node procedure in colon cancer patients

Current staging techniques used for colon cancer are not sufficient and need improvement. Today the techniques being used for lymph node assessment (single section and haematoxylin and eosin staining) are not sufficient to detect micrometastases. A recent meta-analysis showed that the presence of micrometastases are associated with a poorer prognosis.¹¹ There are techniques that are more accurate and capable to detect micrometastases (multisectioning and immunohistochemistry). However, these techniques are expensive and time consuming making it impossible to use for assessment of all lymph nodes found in a resected specimen. But what if we could identify a limited number of lymph nodes which are most likely being affected if metastases already occurred? We could use these accurate techniques to assess a limited number of lymph nodes. The sentinel-lymph-node procedure could offer a solution by identifying those lymph nodes that are most likely being affected. Till today no consensus exists on the validity of the sentinel-lymph-node procedure in colorectal cancer patients. In **Chapter 5** a systematic review and meta-analysis is being presented about the diagnostic performance of the sentinel-lymph-node procedure for nodal status assessment in colorectal cancer. After a search in Embase and PubMed databases, 52 eligible studies were being identified, which included 3767 sentinel-lymph-node procedures (2961 [78.6%] colon and 806 [21.4%] rectal carcinomas). Most tumours 2339 (62.1%) were staged T3 or T4. 1887 (50.1%) of patients were male, 1880 (49.9%) female. Overall analysis showed a low sensitivity for sentinel-lymph-node detection, regardless T stage, localisation or technique used. Additionally a subset of reports with high methodological quality was selected and analysed. Outcomes after analysis of the high quality papers showed that the detection rate and sensitivity in colon cancer

patients reached the same values compared to the sentinel-lymph-node procedure in patients with breast cancer.¹⁴ Because the sensitivity can be increased from 76% (all studies) to 90% and 82% for colon and rectal cancer, respectively, we state that for every patient diagnosed with colon or rectal cancer without clinical evidence of lymph node involvement and metastatic disease a sentinel-lymph-node procedure besides the conventional resection should be considered. The sentinel-lymph-node procedure is very safe, especially when being done ex-vivo. The sentinel-lymph-node procedure performed by the surgeon and detailed assessment of the sentinel node(s) by the pathologist could be part of standard care in patients with colon and rectal cancer worldwide. Due to the detailed assessment of the sentinel node, workload for the pathologist will increase, but the prognostic information of this technique could be significant, with an upstaging of 15%. The percentage of upstaged patients could even be higher including those patients in which positive aberrant sentinel lymph nodes are being detected. Aberrant sentinel lymph nodes are located outside the usual locoregional basins. Unfortunately the prevalence of such aberrant lymph nodes and their status is poorly documented.

Chapter 6. We believe the sentinel-lymph-node procedure could fulfil an important role in future colon cancer treatment. However, considering the results presented in the meta-analysis (**Chapter 5**), technical aspects, such as injection technique and dye characteristics, need to be improved before we can rely on the sentinel-lymph-node procedure for tumour staging completely. The fluorescent technique for example could be an alternative to ink and radioisotope tracers and may overcome many limitations of these conventional techniques. As we experienced in our studies there are several issues which have to be improved. First we observed the problem of dye leakage during the injection of ICG. Our final injection technique was performed by a flexible needle in the subserosal layer around the tumour. Correct positioning of the needle-tip was found to be very difficult. Spillage of ICG results in a fluorescent abdominal cavity and makes it impossible to detect sentinel lymph nodes. Colonoscopic pre- or peroperative injection in the submucosal layer could be a solution. A pilot study studying this technique by preoperative colonoscopic injection is currently recruiting patients. As with blue dye, ICG also has disadvantages. Although the penetration depth in fatty tissue is better than blue dye it is still limited (1.5 cm). We think the combination of radioactive tracers and a new, more fluorescent dye could solve this problem. These new dyes should have better fluorescent characteristics compared to ICG. LI-COR IRDye 800 CW seems to be one of the most promising new dyes. The LI-COR IRDye 800 CW has favourable characteristics compared to the current available dyes. The fluorescence of this dye is supposed to be many times stronger than that of ICG making it better visible in fatty tissue. Ex vivo experiments confirmed this assumption. IRDye 800CW also has a high labelling density which makes IRDye 800CW easy to conjugate with radioactive tracers or monoclonal antibodies which can be interesting for specific tumour targeting and photodetection.

Chapter 7. As stated in chapter 6, sentinel-lymph-node detection could have a future role in colon cancer treatment. As a prerequisite it should be possible to identify and harvest the sentinel lymph node in an accurate, safe, fast and reliable manner. Previous publications showed this is a point of concern.¹³⁻¹⁶ The methods employed for sentinel-lymph-node mapping used till today face some difficulties, which could influence their accuracy in identifying the sentinel lymph node, as also addressed in chapter 6. Like in breast cancer and melanoma, both radio-guided and/or dye-guided imaging has been used for sentinel-lymph-node mapping in patients with colon cancer. However the ink based tracers have a poor tissue

penetration depth and tend to diffuse through the lymph nodes because of their small particle size. Radio-guided imaging faces the problem of signal interference of the injection site that is if the sentinel lymph node is located near the tumour. Another problem when using radio-guided tracers is that the lymph vessels and lymph nodes cannot be visualised real time. In this thesis it has been suggested that near-infrared dyes like indocyanine green may possess the characteristics to overcome these limitations. Indocyanine green is a water-soluble tricarbo-cyanine, which is FDA approved for clinical use. Indocyanine green has a peak spectral absorption at 800-810 nm in blood plasma and blood. Wavelengths in the 800 nm range penetrate relatively deeply into living tissue compared to visible light. This makes it possible to detect the sentinel lymph node accurately in mesenteric adipose tissue. During animal experiments, ICG diluted in 0,9% NaCl only seems not suitable for sentinel lymph node identification. When ICG was dissolved in a NaCl/HSA solution before administration, the dye stayed entrapped in the sentinel lymph node. Confirmatory studies on this topic are on the way. One of the challenges we encountered during our animal experiments was leakage of dye during and after injection. When spilled, the fluorescent dye will stick to all structures in the abdominal cavity. The background fluorescence of the spilled fluorescent material makes sentinel-lymph-node detection very difficult. As described earlier, an alternative method could be submucosal injection during colonoscopy. When leakage occurs the fluorescent dye will drain into the lumen of the colon and not into the abdominal cavity causing less background fluorescence. The group of Marescaux successfully used the technique of Natural Orifice Transluminal Surgery (NOTES) for sentinel biopsy of the colon in six pigs.¹⁵ Methylene blue was used for the detection of the lymph vessels and sentinel lymph nodes. Like discussed earlier this may not be the preferred dye in humans with a fatty mesentery and therefore such positive results are not likely to be expected. More powerful fluorescent dyes are being developed by industries all over the world. Most of them face toxicology studies and therefore won't be available for clinical evaluation the coming years. But there are already a few fluorescent dyes that are commercially available for clinical use.¹⁶ With the development of a laparoscope with near-infrared features, intraoperative visualisation of fluorescent dyes becomes possible. New applications can be explored, for example by using fluorescent dyes conjugated to monoclonal antibodies for intraoperative tumour detection. Imaging guided surgery could become an interesting tool for intraoperative cancer detection and eradication.

Chapter 8. The study presented in this chapter was undertaken to assess the feasibility of sentinel-lymph-node detection and harvesting using the near-infrared dye ICG. As earlier described sentinel-lymph-node mapping using patent blue and radioisotope tracers is noted to have limitations when used in colon cancer patients.^{16,18} Some authors have concluded that the sentinel lymph node concept is not suitable for colon cancer patients, since high false negative ratios were seen.¹⁹⁻²⁰ However, results from the meta-analysis presented in chapter 5, addressing sensitivity of the sentinel-lymph-node procedure in colorectal cancer patients showed favourable results when selecting for high quality studies. Sensitivities as high as 90% with a detection rate of 96% could be achieved.²¹ In addition, recently published studies showed high sensitivity rates when the procedures were accurately performed.^{22,23} As discussed in chapter 7, the tracers used in breast cancer and melanoma patients have limitations. Near-infrared dyes with their unique characteristics could help to overcome these limitations. In chapter 8 we clearly show that lymph nodes in obese patients can be adequately identified using ICG. During animal experiments, presented in chapter 7, we observed the problem of dye leakage. During the procedure in patients we addressed this problem by a pre-injection of saline to assure a correct localisation of the needle. Correct

placement of the needle gives bulging of the colon wall. During the first seven procedures a rigid spinal needle was used for dye injection. Correct positioning of the needle tip was found to be very difficult. During the final six procedures the rigid needle was replaced by a flexible needle. When using a flexible needle, positioning of the needle tip into the colon wall was found to be easier. Intra-abdominal space is limited and manoeuvring of a needle which is flexible showed to be more manageable. Peroperative colonoscopic injection is being studied to be an alternative.²⁴⁻²⁶ In our pilot study tracer material was injected peritumoral. It stands to reason that injection of tracer into the colon wall around the tumour should reveal primary tumour lymphatic drainage. However, there seems to be no consistent drainage pattern for each tumour location. Colon wall vascularisation and lymphatic drainage seems to be complex. Sentinel-lymph-node mapping in large size tumours (>7 cm in diameter) seems to show less favourable results regarding sensitivity. The actual injection site could be situated outside the lymphatic basin on which the tumour drains. Obliteration of the lymph vessels by tumour tissue resulting in an alternative route of lymph flow could also be an explanation. The different injection routes like intratumoral or submucosal injection by per- or preoperative colonoscopy should become a subject for future studies.